## REMARKS

Claims 27-43 are pending and under examination in the above-identified application. Applicant has review the rejections set forth in the Office Action mailed December 19, 2003, and respectfully traverse all grounds for the reasons that follow.

## Rejections Under 35 U.S.C. § 102

The rejection of claims 27-42 is maintained and new claim 43 stands rejected under 35 U.S.C. § 102(e) as anticipated by Fan et al., US 2002/0006617 A1. The Office alleges that Fan et al. is an invention by another and describes all the elements of the claimed invention. Further, the Office alleges that the priority applications for the above-identified application lack support for the claimed invention apparently because they do not explicitly recite RCA (rolling circle amplification). Accordingly, the above-identified application has been accorded a priority date as of the filing date of the parent application, which is March 3, 2000.

While not conceding that Fan et al. constitutes a proper basis for a prior art rejection, Applicant maintains that the benefit of priority should be awarded at least to application serial no. 60/135,053, filed May 20, 1999. The claimed invention is supported in this and other applications to which the benefit of priority is claimed. Such other applications include, for example, application serial no. 60/130,089, filed April 20, 1999; application serial no. 60/135,051, filed May 20, 1999; application serial no. 60/135,123, filed May 20, 1999; application serial no. 60/161,148, filed October 22, 1999; application serial no. 60/160,917, filed October 22, 1999, and application serial no. 60/160,927, filed October 22, 1999. All of such priority applications have a filing date earlier then the earliest filing date listed on Fan et al., which is February 7, 2000.

The claims are directed to a method of detecting an amplification reaction. The method consists of contacting a circularized probe with an amplification primer and an enzyme to form a concatamer amplicon, cleaving the concatamer and contacting the cleavage products

with an array for detection. As set forth below, the priority applications contain each and every element of the claimed invention.

The written description test to determine entitlement to priority of an earlier filed application is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application. *Noelle v. Lederman*, 355 F.3d 1343, 1348 (Fed. Cir. 2004) (*citing Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). The specification must adequately describe the claimed invention so that one skilled in the art can recognize what is claimed. *Enzo Biochem, Inc., v. Gen-Probe Inc.*, 296 F.3d 1316, 1328 (Fed. Cir. 2002).

The priority applications comply with the written description requirement of the first paragraph of § 112 because they describe numerous species of the claimed invention such that one skilled in the art can recognize the full scope of the invention as claimed. Such description demonstrates not only that Applicant contemplated the invention, but also shows that Applicant was in possession of the claimed invention at the time of filing. *Vas-Cath*, 935 F.2d at 1563-64.

The Office appears to rely on an alleged lack of explicit support for RCA amplification amongst the many described amplification methods exemplified in the priority applications. However, there is no controlling authority that has departed from the standard that express support for the claimed invention is not a prerequisite for satisfying the written description requirement. In this regard, the *Vas-Cath* court emphasized:

> A fairly uniform standard for determining compliance with the "written description" requirement has been maintained throughout: "Although [the applicant] does not have to describe exactly the subject matter claimed, ... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

*Id.* at 1563 (quoting *In re Gosteli*, 872 F.2d 1008, 1012, (Fed.Cir.1989) (citations omitted). Applying this standard, *Vas-Cath* held that, under proper circumstances, drawings

alone may provide adequate written description of an invention as required by §112. The court pointed out that elements found in Applicant's claims need not correspond exactly to those disclosed in the parent application. Recently, the *Enzo* court has held that reference to a public deposit of a nucleic acid when its sequence is not otherwise available in written form constitutes adequate written description of a nucleotide sequence. *Enzo*, 296 F.3d at 1325.

The above standard has been applied well before the decision in *Vas-Cath* by the predecessor Court of Customs and Patent Appeals and has been maintained up to the most recent decisions of the Federal Circuit. The court *In re Reynolds* described the principle of inherent written description as follows:

> By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter.

*In re Reynolds*, 443 F.2d 384 (C.C.P.A. 1971); *accord In re Smythe*, 480 F.2d 1376 (C.C.P.A. 1973).

The sufficiency of inherent written description was affirmed even more plainly when the Court of Customs and Patent Appeals stated "[t]o comply with written description, it is not necessary that the application describe the claimed invention in *ipsis verbis*." *Application of Edwards*, 568 F.2d 1349, 1351-52 (C.C.P.A. 1978). Furthermore, the Federal Circuit has very recently reaffirmed that "the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue. "*Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1376, (Fed.Cir. 2002). This well established standard of not requiring express written description for a claimed invention was yet again reaffirmed by the Federal Circuit's statement that "[i]dentity of description is not necessary." *New Railhead Mfg. L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1296 (Fed. Cir. 2002).

Applicant maintains that the specification provides express support sufficient to satisfy the written description requirement for the invention as claimed. Nevertheless, assuming

arguendo, that express support was not provided for every claim element, "[t]he burden . . . rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not in *ipsis verbis* is insufficient." *Application of Edwards*, 568 F.2d at 1354. Applicants respectfully submit that the Office has failed to provide reasons sufficient to meet that burden allocated to it by the Federal Courts.

In this regard, the Office sets forth an apparent *pro forma* rejection based entirely on Applicant's alleged lack of express written description for a species of a claimed element. To support the rejection, the Office chooses an individual claim term, lists seven species of amplification methods described in four of the priority applications, including 10 additional variations of PCR amplification, critiques Applicant's previous arguments only to the extent that they do not appear to provide express support for RCA and alleges lack of *ipsis verbis* support for RCA amplification in the specification. Further, the Office additionally alleges that SDA is limited to a "linear nucleic target" but provides no support for this contention (emphasis original).

As set forth above, in view of the controlling and established federal case law, lack of identity of description is not synonymous with a lack of written description. In other words, the inquiry into whether sufficient written description is provided by the specification cannot properly be based solely on a formulaic approach with no attempt recognize the teachings and guidance of specific embodiments within the specification or the application as a whole. As a result, the Office has not met its burden as to why a description that is not in *ipsis verbis* is insufficient.

In contrast, Applicant has provided specific description of the claimed invention and has further provided adequate teachings and guidance sufficient for one skilled in the art to recognize the invention as claimed. Briefly, Application serial no. 60/135,053, (the '053 application) teaches the use of nucleic acid probes and hybridization for detection of a target sequence. For example, the application teaches on page 3, second full paragraph, that the invention is directed to the detection and quantification of differences or variations of sequences

using bead arrays. The methods of detection include, for example, ligation chain reaction (LCR or OLA), Invader™ technology, single base extension technology, competitive probe binding and sequencing by synthesis. Further, the application explicitly states:

> Many of these methods require a primer nucleic acid (including nucleic acid analogs) that is hybridized to the target sequence to form a hybridization complex, and an enzyme is added that in some way modifies the primer to form a modified primer; generally, the occurrence of the modification depends on the presence or absence of a particular sequence, thus allowing sequence differentiation.

Application at page 3, second full paragraph.

Exemplary primer configurations are further provided for the LCR, CPT (cycling probe technology) and Invader™. The Office confirms the teachings of these and other configurations when it states that the '053 application "teaches detection of mutations using OLA (oligonucleotide ligation assay), Invader technology, competitive probe analysis, pyrosequencing, LCR, CPT (cycling probe technology), PCR, SDA (strand displacement amplification), NASBA (nucleic acid sequence based amplification), and "branched DNA" signal amplification." Further, the application summarizes the probe or primer requirement for detection of a target sequence by teaching:

> Thus, in general, a target nucleic acid is adding [sic] to a reaction mixture that comprises the necessary amplification components, and a modified primer is formed.

and,

> [T]hese techniques can be classified as either target amplification or signal amplification. Target amplification involves the amplification (i.e. replication) of the target sequence to be detected, resulting in a significant increase in the number of target molecules. Target amplification strategies include the polymerase chain reaction (PCR), strand displacement amplification (SDA), and nucleic acid sequence based amplification (NASBA).

Application at page 4, lines 1-3, and third full paragraph, respectfully.

The '053 application further teaches various amplification reaction formats and the use of amplification probes. Exemplary descriptions can be found, for example, at page 4,

paragraph 3 through page 7, and in the section entitled "Invention Disclosure Form" at, for example, pages 1-5. As stated previously, exemplary amplification methods include the polymerase chain reaction (PCR), strand displacement amplification (SDA) and nucleic acid sequence based amplification (NASBA) (page 3, paragraph 3), ligase chain reaction (LCR), cycling probe technology (CPT), Invader™ technology, Q-Beta replicase (QβR) technology, and the use of amplification probes such as branched DNA that result in multiple labeled probes (page 4, lines 1-4). The section entitled "Invention Disclosure Form" further exemplifies amplification of probe and primers using, for example, the oligo ligation assay and allele-specific PCR.

Therefore, the application teaches that numerous amplification methods well known in the art can be used for detecting a target molecule by, for example, amplifying the target or by, for example, amplifying the target probe. Further, the `053 application exemplifies ten additional PCR methodologies that can be employed in the amplification of a target or probe sequence. Except for the general method of PCR, none of the additional ten PCR variations are redundant with the other amplification methodologies described above and taught in the `053 application. Therefore, the application exemplifies a large number of different amplification methods well known in the art that can be used for amplicon formation in the methods of the invention.

The application further teaches at page 4, paragraph 3, and at page 5, paragraph 2, that strand displacement amplification (SDA) can be used in the methods of the invention. Applicant draws the Examiner's attention to the fact that amplification of a circular nucleic acid is a strand displacement amplification methodology. Applicant submits herewith Exhibits A and B showing that strand displacement from a circular template was well known in the art at least as early as 1995. Banér et al., *Nuc. Acid Res.* 26:5073-78 (1998), attached as Exhibit A describes that "[s]everal groups have demonstrated that circular oligonucleotides can support a rolling circle replication (RCR) reaction, analogous to replication mechanisms of several viruses with circular genomes (page 5073, col. 2, paragraph 2, *citing* Fire et al. and Liu et al.). Lizardi et al., *Nat. Genetics* 19:225-32 (1998), attached as Exhibit B describes the use of small circular DNA

template as early as 1995 was well know in the art (page 225, first paragraph, *citing* Fire et al., and Liu et al.). Accordingly, these exhibits exemplify that the use of a circular template is one further amplification method well known in the art.

Applicant has exemplified eight methods of amplification, several of which can include the use of a circular primer for rolling circle amplification. It is likely that Applicant could have recited a number of additional specific amplification methods in the `053 or another priority application. However, recitation of each and every species is not the standard for adequate written description. Rather, all that is required is that Applicant provide sufficient description such that one skilled in the art would recognize in the priority application what is now claimed.

Here, the priority application exemplifies at least eight methods of amplification. The priority application additionally exemplifies ten species of one particular amplification. Therefore, the priority application describes at least 18 different methods of amplification. These descriptions are sufficient to show that Applicant intended all forms of amplification methods well known in the art to be used in the methods of the invention. Rolling circle amplification is one such method well known in the art. The numerous amplification methods and species thereof described in the priority application would provide one skilled in the art with the understanding that other well known amplification methods were intended to be included with in the scope of the invention. Accordingly, these exemplary amplification descriptions show that one skilled in the art would understand that Applicant was in possession of rolling circle amplification at the time the `053 application was filed.

In light of the teachings in the `053 and other priority applications and the remarks above, Applicant contends that the claimed invention is adequately described to be accorded benefit of their filing dates. Accordingly, Applicant respectfully requests that the rejection over Fan et al. be withdrawn.

**Rejections Under 35 U.S.C. § 103**

The rejection of claims 27-41is maintained and new claim 43 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious over Taylor, US 2002/0168645, in view of Walt et al., U.S. Patent No. 6,023,540. Claim 42 stands rejected over the additional reference to Lizardi. In this regard, the Office alleges that Taylor describes the detection of nucleic acids using rolling circle amplification and that Walt et al. describe a microsphere-based system carrying different chemical functionalities, alleged to be capture probes, positioned in wells randomly distributed in an array. The Office concludes that it would have been obvious to combine the detection methods of Taylor on an array of Walt et al. because the fiber optic sensors of Walt et al. support a large number of chemical functionalities and are easy to produce and use.

Taylor provides a specific connection for the detection of RCA amplification products on a microbead array apparently because Taylor describes that RCA products can be attached to microbeads and that a Cantor-type array is a microbead array.

In relying on the assertion that Cantor-type arrays correspond to microbead arrays, the Office cites Examples 1 and 13 of the Cantor patent. These sections do not appear to describe the use of a microbeads for creation and use of an array in combination with an amplification scheme. Instead, Examples 1 and 13 are directed to sequencing by positional hybridization. Determination of a nucleotide sequence does not correspond to amplification of a nucleic acid. Accordingly, Taylor does not suggest the use of a microsphere step in combination with an amplification scheme. Instead, all of the attachment steps described by Taylor are directed to the positional fixing of a capture probe to a solid surface by permanent linkages or to sequencing. See, for example, paragraphs 10, 121-122 and 171. Therefore, the Office's alleged rational fails to support any motivation because there is no evidence that the arrays of Taylor were sufficiently deficient such that one skilled in the art would be motivated to combine with another type of methodology.

Therefore, Applicant maintains that the Office still has failed to provide a showing that the factual basis for providing a motivation to combine can be found any of the

cited references. As set forth in Applicant's previous response, absent the required evidentiary showing of a suggestion, motivation or teaching to combine a rolling circle amplification scheme with microsphere components of an array to achieve the claimed combination amplification reaction, the Office has not established a *prima facie* case of obviousness. Accordingly, Applicant respectfully requests that this ground of rejection be withdrawn.

## CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

Respectfully submitted,

Date: March 19, 2004

David A. Gay
Registration No. 39,200
Telephone: (858) 535-9001
Facsimile: (858) 535-8949

McDERMOTT, WILL & EMERY
4370 La Jolla Village Drive, Suite 700
San Diego, California 92122